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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	PAPER NUMBER
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/694,685	KROLEWSKI ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-54* is/are pending in the application.

4a) Of the above claim(s) *6-8,10-21,23-34,37-46,48,51 and 53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-5,9,22,35,36,47,49,50,52 and 54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/04,7/04, 10/05, 10/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Alignment of SEQ ID NO: 1142 of US Patent 6,979,557; Alignment of SEQ ID NO: 378 of US Patent 6,783,969.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse, in part, of Group I, SEQ ID NO: 1, and SEQ ID NO: 16, in the reply filed on 10/30/2006 is acknowledged. The traversal is on the ground(s) that SEQ ID NOS: 1 is simply longer than SEQ ID NO: 3 and that SEQ ID O: 15 and 16 only differ by a single nucleotide. These arguments have been thoroughly reviewed. The restriction requirement between SEQ ID NOS 1 and 3 has been changed to an election of species. As the claims are not limited to simply SEQ ID NO: 1 or SEQ ID NO: 3, but include oligomers, as well as sequences with particular % identity, search results for SEQ ID NO: 1 would not necessarily provide results for SEQ ID NO: 3. Accordingly, as a proper search for claims directed to SEQ ID NO: 1 is not coextensive with the search required for SEQ ID NO: 3, the restriction requirement between them has been changed to an election of species. SEQ ID NO: 1 is considered the species elected. With regard to SEQ ID NOS 15 and 16, as the sequences are different, and require a different nucleotide at the indicated position in claims 8 and 9, the searches for each are different. Therefore, the restriction requirement has also been changed to an election of species and SEQ ID NO: 16 is considered the species elected.

2. Claim 1 is generic to the following disclosed patentably distinct species: SEQ ID NOS 1 and 3. The species are independent or distinct because they are structurally distinct nucleic acid molecules. Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

3. This application contains claims directed to the following patentably distinct species: SEQ ID NOS 15 and 16. The species are independent or distinct because they are structurally different nucleic acid molecules. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, no claim is generic.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

The remainder of the restriction requirement other than the change to an election of species for SEQ ID NOS: 1/3 and 15/16, is deemed proper and made final.

4. Claims 8, 46, 48, 51, and 53 have been withdrawn from consideration as being drawn to non elected species. Claims 6-7, 10-21, 23-34, and 37-45 are withdrawn from consideration as being drawn to non elected inventions. An action on the merits of claims 1-5, 9, 22, 35, 36, 47, 49, 50, 52, and 54, directed to T2DM1, SEQ ID NO: 1, and 16 follows.

Specification

5. The disclosure is objected to because of the following informalities: the brief description to the drawings for figure 9A-MM does not include a sequence identifier for the sequence in the figure. The figure description should be amended to reflect the sequence identifier in the figure.

Appropriate correction is required.

6. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See for example, page 24, lines 24 which contains an active hyperlink.

Claim Rejections - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 1-5, 9, 22, 35, 36, 47, 49, 50, 52, and 54 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility.

The claimed nucleic acids, vectors, host cells, and arrays are not supported by a specific asserted utility because the disclosed uses of the nucleic acids are not specific and are generally applicable to any nucleic acid. The specification states that the nucleic acid compounds may be used to express a polypeptide, to identify identical, similar or related polynucleotides, in screening assays, in diagnostic assays (page 64), and to determine expression levels. The specification further states that the nucleic acids can be used as probes for detecting identical or related sequences. However, these are non-specific uses that are applicable to nucleic acids in general and not particular or specific to the nucleic acid being claimed.

Further, the claimed nucleic acids, vectors, host cells, and methods of making and using the nucleic acids are not supported by a substantial utility because no substantial utility has been established for the claimed subject matter. For example, a nucleic acid may be utilized to obtain

a protein. The protein could then be used in conducting research to functionally characterize the protein. The need for such research clearly indicates that the protein and/or its function is not disclosed as to a currently available or substantial utility. A starting material that can only be used to produce a final product does not have substantial asserted utility in those instances where the final product is not supported by a specific and substantial utility. In this case, none of the proteins that are to be produced as final products resulting from processes involving claimed nucleic acids have specific and substantial utilities. The research contemplated by applicant(s) to characterize potential protein products, especially their biological activities, does not constitute a specific and substantial utility. Identifying and studying the properties of a protein itself or the mechanisms in which the protein is involved does not define a "real world" context or use. Similarly, the other listed and asserted utilities as summarized above or in the instant specification are neither substantial nor specific due to being generic in nature and applicable to a myriad of such compounds. Neither the specification as filed nor any art of record discloses or suggests any property or activity for the nucleic acid and/or protein compound(s) such that another non-asserted utility would be well established for the compounds.

Although the specification asserts that the nucleic acids and polymorphisms can be used in diagnostic and prognostic assays (page 29), other than teaching the presence of 14 polymorphisms, and teaching that they were found in only 16 chromosomes of 8 type 2 diabetic patients, the specification provides no guidance as to whether the variants themselves are actually associated with type 2 diabetes, or whether the presence of these polymorphisms in diabetic subjects was due to chance. The specification does not teach the allele frequency of these polymorphisms in the normal population, in different racial/ethnic populations, nor does it

teach how many patients were found to have each SNP. Accordingly, it is not predictable, given the limited information in the specification, whether these SNPs or polymorphisms would be expected to be found in the normal as well as type 2 diabetic population. The specification provides insufficient guidance to enable the skilled artisan to use the polymorphisms disclosed as a diagnostic or a marker for type 2 diabetes or any other disease.

Further, although the specification teaches that a BLASTp search was performed for the polypeptide of SEQ ID NO: 2 and was found to share homology with human Diff40, a search revealed, that the homology shared between SEQ ID NO: 2 and human Diff40 was only 35%. The specification also teaches that "T2DM1" is 27.4% identical to the human homolog of the mouse FOSB gene, and 26.3% identical to mouse SEM6C. However, these molecules are all structurally and functionally different, such that the identification of a specific % identity does not provide sufficient guidance to the skilled artisan to be able to reasonably confirm the function of SEQ ID NO: 2, or the nucleic acid encoding it, without further experimentation to actually characterize their functions. As noted by Brenner v. Manson, 383 US 519, 535-536 (1996), "Congress intended that no patents be granted on a chemical compound whose sole "utility" consists of its potential role as an object of use - testing... a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-5, 9, 22, 35, 36, 47, 49, 50, 52, and 54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making an isolated nucleic acid molecule comprising SEQ ID NO: 1 or SEQ ID NO: 16, or an isolated nucleic acid molecule encoding SEQ ID NO: 2, as well as a purified host cell comprising a vector comprising an isolated nucleic acid molecule comprising SEQ ID NO: 1 or SEQ ID NO: 16, or an isolated nucleic acid molecule encoding SEQ ID NO: 2, does not reasonably provide enablement for using such nucleic acids or for making or using the nucleic acids or compositions encompassed by the broad cope of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Further, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

Claims 1-5, 35, 36, 47, and 52 are drawn to isolated nucleic acids which have at least 95% identity to SEQ ID NO: 1, or encode a polypeptide with 95% identity to SEQ ID NO: 2, or which have at least 70% complementarity to a "T2DM1" nucleic acid or nucleic acids capable of detecting a "T2DM1" nucleic acid. The claims (claims 9, 22) are further drawn to sequences which comprise 15 or 20 contiguous nucleotides of SEQ ID NO: 1 or 16, as well as sequences which are only structurally defined by their ability to hybridize to SEQ ID NO: 1 under conditions of high stringency (claims 1, 49, 50). The claims also encompass a nucleic acid molecule comprising SEQ ID NO: 1 as well as SEQ ID NO: 16, and a nucleic acid molecule encoding SEQ ID NO: 2

The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

The amount of direction or guidance and presence and absence of working examples:

These claims represent an extremely large genus of allelic variants, mutants, and homologs of SEQ ID NO: 1 from any source. The specification teaches the sequence of the long from of T2DM1: SEQ ID NO: 1, the short form: SEQ ID NO: 3, as well as short fragments containing 14 polymorphisms that were found inT2DM1. However, the specification does not define the structural and functional attributes that a sequence is required to possess for the skilled artisan to be able to predictably determine what is a "T2DM1" nucleic acid vs not. The function of these sequences is not taught. Therefore, one of skill in the art would not be able to determine if a sequence was a T2DM1 sequence other than by SEQ ID NO:.

The specification teaches that a BLASTp search was performed for the polypeptide of SEQ ID NO: 2 and was found to share homology with human Diff40. However, a search revealed, that the homology shared between SEQ ID NO: 2 and human Diff40 was only 35%. The specification teaches that "T2DM1" is 27.4% identical to the human homolog of the mouse FOSB gene, and 26.3% identical to mouse SEM6C. However, these molecules are all structurally and functionally different, such that the identification of a specific % identity does not provide sufficient guidance to the skilled artisan to be able to determine the function of SEQ ID NO: 2.

The teachings in the specification indicate that the claimed invention is intended to encompass natural and non-natural variants, homologs, and orthologs, which have encode both functional and nonfunctional proteins (pages 39-40). The specification teaches 14 polymorphisms, however, the specification does not teach whether the disclosed polymorphisms alter the function of the encoded protein or not. The specification particularly does not identify any variants having similar, increased or decreased activity as compared to the polypeptide encoded by SEQ ID NO: 1 or SEQ ID NO: 3. The specification does not disclose any additional variants of the polypeptide encoded by SEQ ID NO: 2.

Preferred variants are asserted to be those correlated with susceptibility to type 2 diabetes (page 40, line 23). However, other than teaching the presence of 14 polymorphisms, and teaching that they were found in only 16 chromosomes of 8 type 2 diabetic patients, the specification provides no guidance as to whether the variants themselves are actually associated with type 2 diabetes, or whether the presence of these polymorphisms in diabetic subjects was due to chance. The specification does not teach the allele frequency of these polymorphisms in

the normal population, in different racial/ethnic populations, nor does it teach how many patients were found to have each SNP. Accordingly, it is not predictable, given the limited information in the specification, whether these SNPs or polymorphisms would be expected to be found in the normal as well as type 2 diabetic population. The specification provides insufficient guidance to enable the skilled artisan to use the polymorphisms disclosed as a diagnostic or a marker for type 2 diabetes.

Further, the claims encompass host cells in vivo. The specification asserts the use of cells as pharmaceutical preparations in gene therapy, however, the specification does not provide any teaching or guidance regarding any therapy using the claimed nucleic acids or host cells. The specification provides no guidance on any particular therapy, routes or modes of administration, etc for one of skill in the art to predictably determine a therapeutic use or application for the claimed products.

The state of the prior art and the predictability or unpredictability of the art:

With regard to the teachings of alignments with other proteins, such evidence is not found to predictably establish the function of the polypeptide of SEQ ID NO: 2, as exemplified by the teachings of the prior art. For example, Fetrow teaches (Fetrow et al., J. Mol. Biol., vol. 282, pp 703-711, 1998) that although function prediction by homology to previously characterized proteins is extremely successful and is fast, cheap and reliable, there are several problems that limit its potential utility, one of which is that sequence homology does not guarantee functional similarity (p 704, col. 1, 1st full paragraph). Fetrow teaches that "threading"(analysis using structure prediction tools) can identify topological cousins, that is,

protein families such as the α/β barrels with similar structures, but dissimilar functions. Fetrow teaches using a three dimensional descriptor of the active site of a protein, termed "fuzzy functional form" (FFF) and argues that threading alone is not enough to provide the required information about function because it has been shown that pairs of proteins can have similar structures but unrelated functions (p. 706, col. 2, last para). Fetrow teaches that because such topological cousins exist, knowledge of the structure is not equivalent to identification of protein function. Skolnick (Skolnick and Fetrow, TIBTECH, January 2000, vol. 18, pp 34-39) teaches (p. 35, "Box 1") that a common protein characteristic that makes functional analysis based only on homology especially difficult is the tendency of proteins to be multifunctional. Skolnick teaches that for example, lactate dehydrogenase binds NAD, substrate, and zinc and performs a redox reaction and that each of these occurs at different functional sites that are in close proximity and the combination of all four sites creates the fully functional proteins. Skolnick also teaches that the serine threonine phosphatase superfamily is a prime example of the difficulties of using standard sequence analysis to recognize the multiple functions found in single proteins. Skolnick teaches that this large protein family is divided into a number of subfamilies, all of which contain an essential phosphatase active site. He teaches that subfamilies 1, 2A and 2b exhibit 40% or more sequence identity between them, however each of these subfamilies is apparently regulated differently by the cell and observation suggest that there are different functional sites at which regulation can occur. Skolnick teaches that because the sequence identity between subfamilies is so high, standard sequence similarity methods could easily misclassify new sequences as members of the wrong subfamily if the functional sites are not carefully considered. Further, it is noted that the degree of identity to each molecule set forth

in the specification is low. Berendsen teaches (Berendsen, Science, vol. 282, pages 642-643, 1998) teaches that although homology modeling provides information regarding known structures, the methods are only effective for 25% of proteins for which the amino acid sequence is known, and that if homology drops below 25%, the reliability of database oriented methods drops to nearly zero. Therefore, the art specifically teaches, that sequence alignment alone does not necessarily provide a predictable correlation between the structure and specific function of a protein. Additionally, the function of each of the molecules disclosed in the specification is different, such that the disclosure of BLAST search results with low levels of homology does not provide the skilled artisan with a predictable function or readily apparent use for the claimed nucleic acid molecules. The teachings with regard to Diff40 at page 25 of the specification, do not provide the skilled artisan with any predictable function for SEQ ID NO: 2 or 4, nor does it provide any guidance as to the association of such proteins, the nucleic acids encoding them, or variants with regard to type 2 diabetes.

Although the specification teaches that the polymorphism in SEQ ID NO: 16 can be used in diagnostic and prognostic methods, as noted above, the specification does not provide any guidance as to whether the SNP disclosed in SEQ ID NO: 16, or any of the other SNPs, is associated with or a marker for type 2 diabetes. The detection of new polymorphisms is an entirely unpredictable art which is empirical in nature, and once these polymorphisms are detected, their association with a phenotype must be established before they can be used in any predictive manner. There is a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states, as well as drug or therapeutic response. However, the art is highly unpredictable with regard to the functionality of

polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state, a physiological state, or drug metabolism or response. For example, Hacker et al. teaches that they were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Hacker et al; Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the p-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 1998; 281 (5384):1787-1789). Further, in some cases where multiple polymorphisms were identified in a gene, some of these were demonstrated to be disease associated and some were not. For example, Blumenfeld et al. (WO 99/52942) disclose a number of polymorphisms in the FLAP gene. While Blumenfeld et al. were able to demonstrate that some of these polymorphisms are associated with patients having asthma Blumenfeld et al found that some of these polymorphisms are not (see Figure 3). For example, the marker 10-35/390 was demonstrated to be associated with asthma, with a p value of 0.00229, while the marker 10-33/327 was determined not to have a statistical association with asthma (p=0.294). In the instant case, the specification only provides information that the variant exists, but provides no guidance that it has any effect or is associated with or is a marker for type 2 diabetes. Further, even if an association is demonstrated between a single polymorphism within a gene and a phenotype, it is

not necessarily a predictor that a different polymorphism within a gene will also have the same predictive ability. In the instant case, as the specification does not teach if the polymorphisms alter the sequence of the encoded protein (SEQ ID NO: 2) and further because the specification does not teach the function of the protein, it is unpredictable as to whether any other polymorphism would have any phenotypic effect, let alone what that phenotypic effect might be. Additionally, in the instant invention, a high level complexity and unpredictability also exists in simply establishing that within a given combination of SNPs, differences observed with regard to phenotype are not due to chance alone, because no teaching of any statistically significant association is taught, nor does the specification provide any guidance as to the allele frequencies of each polymorphism in ethnically matched patients and normal controls. For example, it is unclear if there was a lack of statically significant results, and if so, if it was due to small sample size (see Nature Genetics, vol. 22, pages 1-2, 1999; "Freely Associating").

The level of skill in the art:

The level of skill in the art is deemed to be high.

The quantity of experimentation necessary:

Given the lack of guidance in the specification and as exemplified by the teachings of the art, a large amount of unpredictable trial and error experimentation would be required of the skilled artisan to make and use the broadly claimed invention. The skilled artisan would first be required to determine the function of the claimed nucleic acids to determine if there was any association with type 2 diabetes. Additionally, the skilled artisan would be required to perform a

large study of patients and ethnically matched controls to determine if the presence of the claimed polymorphism was diagnostic for, prognostic for, or a marker for type 2 diabetes or if the polymorphism also exists in the general population with similar allelic frequency. The experimentation required by the skilled artisan amounts to a research project with each of the intervening steps not being guaranteed of a successful or predictable result. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform make and use nucleic acids encompassed by the claims.

11. Claims 1-5, 9, 22, 35-36, 47, 49, 50, and 52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-5, 35, 36, 47, and 52 are drawn to isolated nucleic acids which have at least 95% identity to SEQ ID NO: 1, or encode a polypeptide with 95% identity to SEQ ID NO: 2, or which have at least 70% complementarity to a "T2DM1" nucleic acid or nucleic acids capable of detecting a "T2DM1" nucleic acid. The claims (claims 9, 22) are further drawn to sequences which comprise 15 or 20 contiguous nucleotides of SEQ ID NO: 1 or 16, as well as sequences

which are only structurally defined by their ability to hybridize to SEQ ID NO: 1 under conditions of high stringency (claims 1, 49, 50). These claims represent an extremely large genus of allelic variants, mutants, and homologs of SEQ ID NO: 1 from any source. The specification teaches the sequence of the long from of T2DM1: SEQ ID NO: 1, the short form: SEQ ID NO: 3, as well as short fragments containing 14 polymorphisms that were found inT2DM1. However, the specification does not define the structural and functional attributes that a sequence is required to possess to be considered a "T2DM1" nucleic acid. The function of these sequences is not taught. Therefore, one of skill in the art would not be able to determine if a sequence was a T2DM1 sequence other than by SEQ ID NO:.

The specification teaches that a BLASTp search was performed for the polypeptide of SEQ ID NO: 2 and was found to share homology with human Diff40. However, a search revealed, that the homology shared between SEQ ID NO: 2 and human Diff40 was only 35%. The specification teaches that "T2DM1" is 27.4% identical to the human homolog of the mouse FOSB gene, and 26.3% identical to mouse SEM6C. However, these molecules are all structurally and functionally different, such that the identification of a specific % identity does not provide sufficient guidance to the skilled artisan to be able to determine the function of SEQ ID NO: 2. The teachings in the specification indicate that the claimed invention is intended to encompass natural and non-natural variants, homologs, and orthologs, which have encode both functional and nonfunctional proteins (pages 39-40). Preferred variants are asserted to be those correlated with susceptibility to type 2 diabetes. However, other than teaching the presence of 14 polymorphisms, and teaching that they were found in only 16 chromosomes of subjects with type 2 diabetes, the specification provides no guidance as to whether the variants themselves are

actually correlated with type 2 diabetes, or are due to chance alone. The specification does not disclose any additional variants of the polypeptide encoded by SEQ ID NO: 2, nor does the specification teach whether the disclosed polymorphisms alter the function of the encoded protein or not. The specification particularly does not disclose any variants having similar, increased or decreased activity as compared to the polypeptide encoded by SEQ ID NO: 1 or SEQ ID NO: 3. Accordingly, while isolated polynucleotides comprising SEQ ID NO: 1, SEQ ID NO: 3, and consisting of SEQ ID NO: 16, as well as nucleic acids encoding the polypeptide of SEQ ID NO: 2 or 4, meet the written description requirements of 35 U.S.C. 112, first paragraph, the specification does not disclose and fully characterize the genus of nucleic acid molecules encompassed by the broadly claimed invention.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...' requires a precise definition,

such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the only members of the claimed genus of polynucleotides with the disclosed % identity or complementarity or ability to hybridize under conditions of high stringency to SEQ ID NO: 1 which have been defined in terms of structure, are SEQ ID NO: 1, SEQ ID NO: 3, and 14 polymorphisms.

It is then determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g., in terms of a specific functional activity). In the instant case, no such identifying characteristics have been provided for any additional variants. While one could contemplate a nucleic acid substitution, deletion or addition at each and every position in SEQ ID NO: 1, such alterations are not considered to be equivalent to specific naturally occurring variants, homologs and orthologs of the polypeptide encoded by SEQ ID NO: 1. Accordingly, knowledge of the sequence of SEQ ID NO: 1 and the putative amino acid sequence of SEQ ID NO: 2 does not allow the skilled artisan to envision all of the contemplated polymorphisms, functional variants, splice variants, homologs and orthologs encompassed by the claimed genus of polypeptides. Therefore, Applicants have not provided sufficient evidence that they were in possession, at the time of filing, of the invention as it is broadly claimed and thus the written description requirement has not been satisfied for the claims as they are broadly written. Applicants attention is drawn to the Guidelines for the Examination of Patent Applications under 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 3-5 recite the term 'host' cell, however it is not clear if the claim intends it to encompass a host organism, such as an animal or not. From applicant's election of group I, distinct from the transgenic animal claims in group VII, it appears that the claim is intended to refer to a purified cell. It is suggested that the claims be amended to recite the term "purified" to clearly distinguish it from an animal.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

15. Claims 1-5, 22, 35, 36, 47, 49, 50, 52 and 54 are rejected under 35 U.S.C. 102(e) as being anticipated by Tang (Tang et al; US Patent 6,783,969)

Tang teaches a nucleotide sequence which is 98% identical to the nucleotide sequence of SEQ ID NO: 1, and has 96.5% identity over the full length of SEQ ID NO: 1 (SEQ ID NO: 378 of Tang; alignment provided). Tang teaches vectors and host cells, including mammalian and

human host cells comprising the sequence (col. 15, lines 10-30; col. 20, lines 36-55), sequences that hybridize to such under highly stringent conditions (col. 10, lines 33-40). Tang teaches primers and probes (col. 12, lines 40-44) as well as fragments of greater than 17 nucleotides (col. 13, line 1), arrays comprising oligomers (col. 31, lines 25-36), as well as compositions (col. 52, lines 55) and multiple antisense sequences (col. 30-lines 43-col. 31).

16. Claims 1, 35, 36, 47, and 52 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Fodor (US Pregrant Publication 20010053519).

Fodor teaches an array of all possible 10 mer nucleic acid sequences (example 2). The claims, for example claim 1, do not require that the recited % identity be over the full length of the molecule. The claims encompass a large genus of nucleic acid molecules which can have 70% (claim 36), or 95% (claim 1, claim 47) identity to SEQ ID NO: 1, as well as molecules which have no recited structural limitations (claim 35). The genus of nucleic acids taught by Fodor anticipates the genus of claimed nucleic acid molecules.

17. Claims 1, 35, 36, 47, and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by Brennan (US Patent 5,474,796).

Brennan teaches an array of all possible 10 mer nucleic acid sequences (see cols 9-10). The claims, for example claim 1, do not require that the recited % identity be over the full length of the molecule. The claims encompass a large genus of nucleic acid molecules which can have 70% (claim 36), or 95% (claim 1, claim 47) identity to SEQ ID NO: 1, as well as molecules

which have no recited structural limitations (claim 35). The genus of nucleic acids taught by Brennan anticipates the genus of claimed nucleic acid molecules.

18. Claims 1-4, 9, 22, 35-36, 47, 49-50, and 52 are rejected under 35 U.S.C. 102(e) as being anticipated by Isogai (Isogai et al; US Patent 6,979,557).

Isogai teaches an isolated nucleic acid molecule (SEQ ID NO: 1142) which comprises a nucleic sequence which is 100% identical to SEQ ID NO: 1 (alignment provided). Isogai teaches vectors and host cells, including mammalian host cells comprising the sequence (col. 33), sequences that hybridize to such under highly stringent conditions (col. 31, lines 1-5). Isogai teaches primers and probes (col. 12, lines 40-44) as well as fragments of greater than 15 nucleotides (col. 31, lines 63-67), arrays and compositions comprising nucleic aids (library), and multiple antisense sequences (col. 32, lines 39-45).

19. Claims 1-3, 22, 47, and 49-50 are rejected under 35 U.S.C. 102(b) as being anticipated by Genbank Accession number BF688656 (Dec. 2000).

With regard to claims 1-3 and 47. Genbank Accession number BF688656 teaches a sequence which has 99.8% identity to SEQ ID NO: 1 (alignment provided). The sequence is taught to have been a clone and comprised in a vector, pOTB7, and in a host cell: DH10B. With regard to claim 22, the sequence comprises 15 nucleotides of SEQ ID NO: 1. With regard to claims 49-50, the Tm of the sequence is over 80 deg C and would be expected to hybridize under the conditions set forth in the claims.

Conclusion

20. No claims are allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jehanne Sitton

Jehanne Sitton
Primary Examiner
Art Unit 1634
1/18/07

Alignment for Sequence 1142 of US Patent 6,979,557

RESULT 2
US-10-094-749-1142/c
; Sequence 1142, Application US/10094749
; Publication No. US20030219741A1
; GENERAL INFORMATION:
; APPLICANT: ISOGAI, TAKAO
; APPLICANT: SUGIYAMA, TOMOYASU
; APPLICANT: OTSUKI, TETSUJI
; APPLICANT: WAKAMATSU, AI
; APPLICANT: SATO, HIROYUKI
; APPLICANT: ISHII, SHIZUKO
; APPLICANT: YAMAMOTO, JUN-ICHI
; APPLICANT: ISONO, YUUKO
; APPLICANT: HIO, YURI
; APPLICANT: OTSUKA, KAORU
; APPLICANT: NAGAI, KEIICHI
; APPLICANT: IRIE, RYOTARO
; APPLICANT: TAMECHIKA, ICHIRO
; APPLICANT: SEKI, NAOHIKO
; APPLICANT: YOSHIKAWA, TSUTOMU
; APPLICANT: OTSUKA, MOTOYUKI
; APPLICANT: NAGAHARI, KENJI
; APPLICANT: MASUHO, YASUHIKO
; TITLE OF INVENTION: NOVEL FULL-LENGTH cDNA
; FILE REFERENCE: 084335/0160
; CURRENT APPLICATION NUMBER: US/10/094,749
; CURRENT FILING DATE: 2002-03-12
; PRIOR APPLICATION NUMBER: 60/350,435
; PRIOR FILING DATE: 2002-01-24
; PRIOR APPLICATION NUMBER: JP 2001-328381
; PRIOR FILING DATE: 2001-09-14
; NUMBER OF SEQ ID NOS: 3381
; SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 1142
; LENGTH: 2698
; TYPE: DNA
; ORGANISM: Homo sapiens
US-10-094-749-1142

Query Match 100.0%; Score 40; DB 7; Length 2698;
Best Local Similarity 100.0%; Pred. No. 4.7e-14;
Matches 40; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

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Qy          1 AAACAGGGACAGCTCATCCGGGGCGAAGTCGGCATTGAGG 40
              ||||||||||||||||||||||||||||||||||||||||
Db       2076 AAACAGGGACAGCTCATCCGGGGCGAAGTCGGCATTGAGG 2037
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Alignment for Sequence 378 from USPatent 6,783,969

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RESULT 1
AR578202
LOCUS       AR578202                4449 bp    DNA     linear   PAT 14-DEC-2004
DEFINITION  Sequence 378 from patent US 6783969.
ACCESSION   AR578202
VERSION     AR578202.1  GI:56580998
KEYWORDS    .
SOURCE      Unknown.
  ORGANISM  Unknown.
            Unclassified.
REFERENCE   1  (bases 1 to 4449)
  AUTHORS   Tang,Y.T., Goodrich,R.W., Asundi,V. and Drmanac,R.T.
  TITLE     Cathepsin V-like polypeptides
  JOURNAL   Patent: US 6783969-A 378 31-AUG-2004;
            Nuvelo, Inc.; Sunnyvale, CA
FEATURES             Location/Qualifiers
     source          1. .4449
                     /organism="unknown"
                     /mol_type="genomic DNA"
ORIGIN

  Query Match             96.5%;  Score 4063;  DB 2;  Length 4449;
  Best Local Similarity   98.0%;  Pred. No. 0;
  Matches 4156;  Conservative    0;  Mismatches    0;  Indels   83;  Gaps    1;

Qy          56 GCCAGATAAGAGTCCCGGCTGCATTATCAGAGCCCGGCAGGGCACCGGCCTCCCTGCACC 115
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         107 GCCAGATAAGAGTCCCGGCTGCATTATCAGAGCCCGGCAGGGCACCGGCCTCCCTGCACC 166

Qy         116 AGAAGGAAGACTCGGGGCGCAGCAGGTCCTCAAGGCGATCTTCCCAGAGAGCGGGACCAG 175
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         167 AGAAGGAAGACTCGGGGCGCAGCAGGTCCTCAAGGCGATCTTCCCAGAGAGCGGGACCAG 226

Qy         176 CGGCTGGTGGCCAGTGTGGATGGAATTTGCAGAGCCCTAGCTCGAGTCCGGGAGTCCCGG 235
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         227 CGGCTGGTGGCCAGTGTGGATGGAATTTGCAGAGCCCTAGCTCGAGTCCGGGAGTCCCGG 286

Qy         236 GCCAGATGGGAGCAGACGCTTGCTGGCGGCAATAGGGAAAGTGAGGCAGCTGCAAGGAGG 295
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         287 GCCAGATGGGAGCAGACGCTTGCTGGCGGCAATAGGGAAAGTGAGGCAGCTGCAAGGAGG 346

Qy         296 GCGGCGGGACTGCACTCGAGTGTCCAGACCTGCTCGATGGTGACCACCATGTCGGTGAGG 355
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         347 GCGGCGGGACTGCACTCGAGTGTCCAGACCTGCTCGATGGTGACCACCATGTCGGTGAGG 406

Qy         356 TTGCGGTTCCTGTCCCCTGGGGACACAGGGGCCGTGGGGGTCGTGGGCCGGAGCGCCTCC 415
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         407 TTGCGGTTCCTGTCCCCTGGGGACACAGGGGCCGTGGGGGTCGTGGGCCGGAGCGCCTCC 466

Qy         416 TTCGCAGGCTTCAGCAGTGCACAGAGCCGGAGGATCGCAAAGTCCATCAACAGGAACTCC 475
               |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         467 TTCGCAGGCTTCAGCAGTGCACAGAGCCGGAGGATCGCAAAGTCCATCAACAGGAACTCC 526

Qy         476 GTGAGATCGCGAATGCCTGCAAAATCCTCCAAGATGTACGGCACGCTGCGGAAGGGGTCG 535
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Db         527 GTGAGATCGCGAATGCCTGCAAAATCCTCCAAGATGTACGGCACGCTGCGGAAGGGGTCG 586
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Qy       536 GTCTGTGCAGACCCGAAGCCCCAGCAGGTGAAGAAGATCTTCGAAGCATTGAAAAGAGGC 595
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Db       587 GTCTGTGCAGACCCGAAGCCCCAGCAGGTGAAGAAGATCTTCGAAGCATTGAAAAGAGGC 646

Qy       596 CTCAAGGAGTATCTGTGTGTGCAGCAGGCTGAGCTGGACCACCTGTCTGGACGCCACAAA 655
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       647 CTCAAGGAGTATCTGTGTGTGCAGCAGGCTGAGCTGGACCACCTGTCTGGACGCCACAAA 706

Qy       656 GACACCAGGAGGAATTCCAGGCTGGCTTTCTATTATGACCTGGACAAGCAAACGCGCTGT 715
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       707 GACACCAGGAGGAATTCCAGGCTGGCTTTCTATTATGACCTGGACAAGCAAACGCGCTGT 766

Qy       716 GTGGAAAGGCACATTCGGAAGATGGAGTTTCACATCAGCAAGGTGGATGAGCTGTACGAG 775
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       767 GTGGAAAGGCACATTCGGAAGATGGAGTTTCACATCAGCAAGGTGGATGAGCTGTACGAG 826

Qy       776 GACTACTGCATCCAGTGCCGCCTGCGCGACGGCGCCTCCAGCATGCAGCGGGCCTTCGCC 835
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       827 GACTACTGCATCCAGTGCCGCCTGCGCGACGGCGCCTCCAGCATGCAGCGGGCCTTCGCC 886

Qy       836 CGGTGCCCCCCGAGCCGCGCAGCCCGAGAGAGCCTGCAGGAGCTGGGCCGCAGCCTGCAC 895
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       887 CGGTGCCCCCCGAGCCGCGCAGCCCGAGAGAGCCTGCAGGAGCTGGGCCGCAGCCTGCAC 946

Qy       896 GAGTGCGCCGAGGACATGTGGCTCATCGAGGGGGCCCTGGAGGTTCACCTGGGCGAGTTC 955
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       947 GAGTGCGCCGAGGACATGTGGCTCATCGAGGGGGCCCTGGAGGTTCACCTGGGCGAGTTC 1006

Qy       956 CACATCAGGATGAAAGGCTTGGTGGGCTACGCACGCCTCTGTCCCGGAGACCACTATGAG 1015
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      1007 CACATCAGGATGAAAGGCTTGGTGGGCTACGCACGCCTCTGTCCCGGAGACCACTATGAG 1066

Qy      1016 GTGCTCATGCGTCTGGGCCGCCAGCGTTGGAAGCTCAAGGGTCGGATCGAGTCAGATGAC 1075
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      1067 GTGCTCATGCGTCTGGGCCGCCAGCGTTGGAAGCTCAAGGGTCGGATCGAGTCAGATGAC 1126

Qy      1076 AGCCAGACCTGGGACGAAGAGGAGAAGGCCTTCATCCCCACGCTGCATGAGAACCTGGAC 1135
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      1127 AGCCAGACCTGGGACGAAGAGGAGAAGGCCTTCATCCCCACGCTGCATGAGAACCTGGAC 1186

Qy      1136 ATCAAGGTGACGGAGTTGCGGGGCCTGGGCTCGCTGGCTGTGGGTGCAGTGACGTGTGAC 1195
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      1187 ATCAAGGTGACGGAGTTGCGGGGCCTGGGCTCGCTGGCTGTGGGTGCAGTGACGTGTGAC 1246

Qy      1196 ATCGCCGACTTCTTCACGACGCGGCCGCAGGTCATCGTGGTGGACATCACGGAGTTGGGT 1255
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      1247 ATCGCCGACTTCTTCACGACGCGGCCGCAGGTCATCGTGGTGGACATCACGGAGTTGGGT 1306

Qy      1256 ACCATCAAGCTGCAGCTGGAGGTGCAGTGGAACCCGTTTGATACTGAGAGCTTCCTGGTG 1315
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      1307 ACCATCAAGCTGCAGCTGGAGGTGCAGTGGAACCCGTTTGATACTGAGAGCTTCCTGGTG 1366

Qy      1316 TCACCCAGCCCCACGGGCAAGTTTTCTATGGGCAGCAGGAAGGGCTCCTTGTACAACTGG 1375
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      1367 TCACCCAGCCCCACGGGCAAGTTTTCTATGGGCAGCAGGAAGGGCTCCTTGTACAACTGG 1426

Qy      1376 ACACCCCCGAGCACCCCCAGCTTCCGGGAGAGATACTACCTGTCTGTCCTACAGCAGCCA 1435
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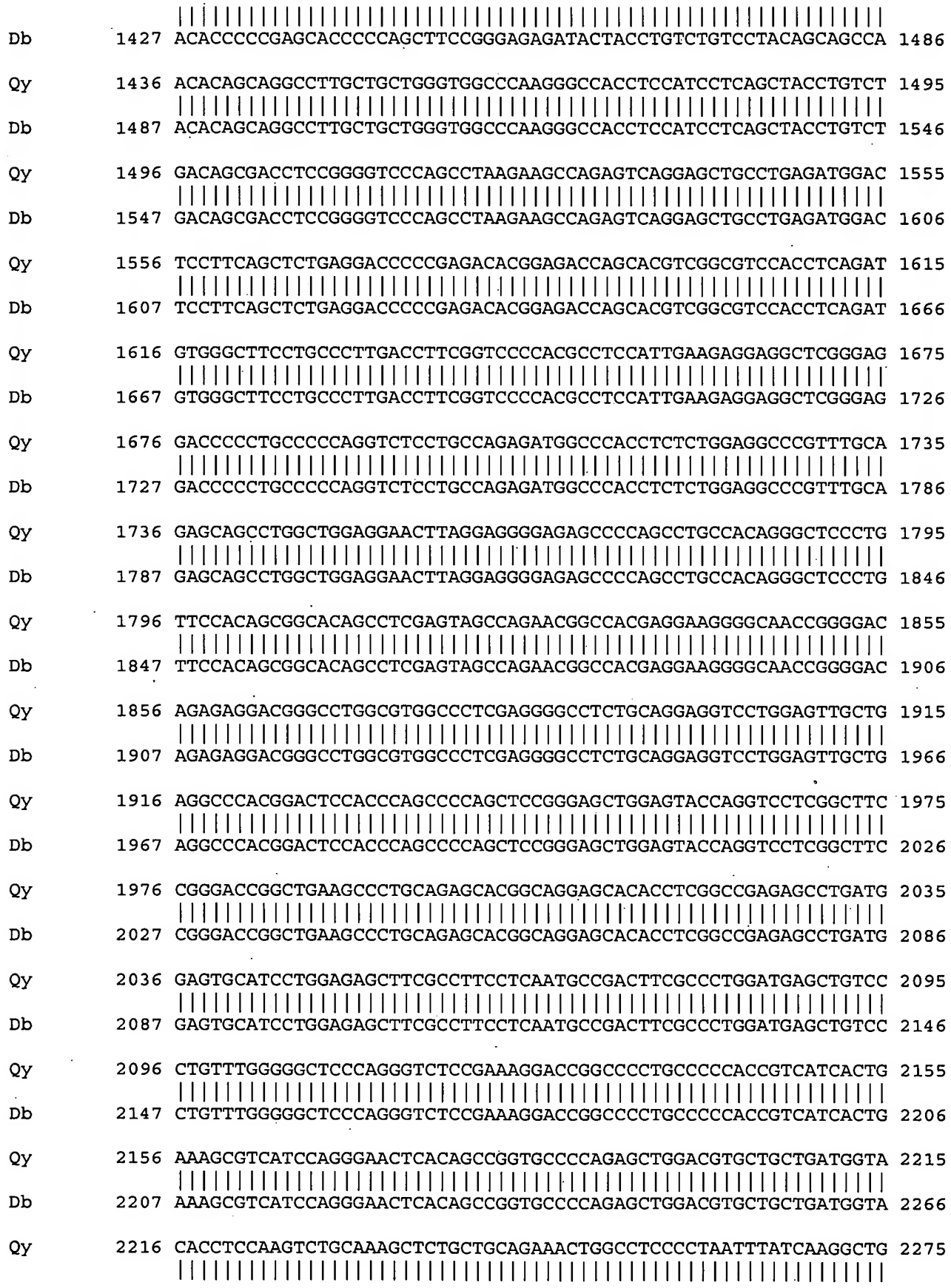

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Db       2267 CACCTCCAAGTCTGCAAAGCTCTGCTGCAGAAACTGGCCTCCCCTAATTTATCAAGGCTG 2326

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             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2327 GTCCAGGAATGCCTCCTGGAAGAAGTGGCACAGCAAAAGCACGTTCTGGAGACACTTTCT 2386

Qy       2336 GTCCTTGACTTTGAGAAGGTCGGCAAGGCAACATCCATTGAAGAGA-------------- 2381
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Db       2387 GTCCTTGACTTTGAGAAGGTCGGCAAGGCAACATCCATTGAAGAGAGTCCTAGTGGAGGG 2446

Qy       2382 ------------------------------------------------------------ 2381

Db       2447 AAACCTTTCGGGTCCTTGTCATGTGCTCTCCCCGAGTCACCATTCAGGTTTCTGAACTGG 2506

Qy       2382 ---------TCATCCCACAGGCCTCGCGGACGAAGGGGTGCCTGAAGCTGTGGAGAGGGT 2432
                       ||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2507 GGCTTTCAGTCATCCCACAGGCCTCGCGGACGAAGGGGTGCCTGAAGCTGTGGAGAGGGT 2566

Qy       2433 GCACAGGGCCTGGCAGGGTCCTGTCCTGCCCTGCCACGACGCTGCTGAACCAGCTCAAGA 2492
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2567 GCACAGGGCCTGGCAGGGTCCTGTCCTGCCCTGCCACGACGCTGCTGAACCAGCTCAAGA 2626

Qy       2493 AAACCTTCCAGCACAGAGTCAGAGGGAAGTACCCAGGACAGCTGGAAATAGCGTGCCGCA 2552
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Qy       2553 GGCTCCTGGAGCAGGTGGTCAGCTGTGGTGGGCTGCTCCCCGGAGCTGGGCTCCCAGAAG 2612
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Qy       2673 TGGAGAAGCACTTCACCCAGCTCACCAAGGAAGTGACACTCATCGAGGAGCTTCACTGTG 2732
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Qy       2733 CGGGACAGGCCAAGGTGGTCCGGAAGCTGCAGGGGAAGCGGCTGGGCCAGCTCCAGCCTC 2792
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Qy       2793 TGCCCCAGACCTTAAGAGCCTGGGCGCTGCTCCAGCTGGACGGCACTCCGAGGGTGTGCA 2852
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2927 TGCCCCAGACCTTAAGAGCCTGGGCGCTGCTCCAGCTGGACGGCACTCCGAGGGTGTGCA 2986

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Qy       2973 TAGCGCTCAAACACCTCAAGGGCATTGAAAGCATCGACCAGACTGCCAGCCTGTGCCAGT 3032
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Qy       3033 CTGACCTGGAGGCCGTGCGGGCGGCAGCCCGGGAAACCACACTGTCGTTCGGTGAAAAAG 3092
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Db       3167 CTGACCTGGAGGCCGTGCGGGCGGCAGCCCGGGAAACCACACTGTCGTTCGGTGAAAAAG 3226

Qy       3093 GACGGTTAGCTTTTGAGAAGATGGACAAGCTCTGCTCAGAACAAAGAGAAGTCTTTTGCC 3152
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3227 GACGGTTAGCTTTTGAGAAGATGGACAAGCTCTGCTCAGAACAAAGAGAAGTCTTTTGCC 3286

Qy       3153 AGGAGGCAGATGTTGAAATCACAATATTTTAAAAAATCCTGGCTGATGAGCACAAATCTC 3212
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Db       3287 AGGAGGCAGATGTTGAAATCACAATATTTTAAAAAATCCTGGCTGATGAGCACAAATCTC 3346

Qy       3213 ACATCGTTTTTTTTGCTGCTGCCCAGCCTGGACATAGCCTGCACTCTGGGTAATGGTGCT 3272
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Db       3347 ACATCGTTTTTTTTGCTGCTGCCCAGCCTGGACATAGCCTGCACTCTGGGTAATGGTGCT 3406

Qy       3273 GTGCACTCCTCCAGGAGTGTGAGCTGCCCAGAGCTCTACCTGAGACTCCGGCCATTGACC 3332
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3407 GTGCACTCCTCCAGGAGTGTGAGCTGCCCAGAGCTCTACCTGAGACTCCGGCCATTGACC 3466

Qy       3333 CAGCCCCAGGGCATGGGCTGGTCTTTTGTACAGAGGCAGAAAAAAGCAAGGCAAAGGTAC 3392
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3467 CAGCCCCAGGGCATGGGCTGGTCTTTTGTACAGAGGCAGAAAAAAGCAAGGCAAAGGTAC 3526

Qy       3393 AGCATTCCAGGGGCTGCACGGCCTCAACAGAGCGCTCAACTTCTGGCTGAGGGTCTGTGT 3452
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3527 AGCATTCCAGGGGCTGCACGGCCTCAACAGAGCGCTCAACTTCTGGCTGAGGGTCTGTGT 3586

Qy       3453 GACCTTCCCCGAGATGCAGAGCTGAGCCAAACTAGGTGGCCACCTACAAAAGGGCCAAGG 3512
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3587 GACCTTCCCCGAGATGCAGAGCTGAGCCAAACTAGGTGGCCACCTACAAAAGGGCCAAGG 3646

Qy       3513 CCAGGCAAGTTGAGGCCCTAAATAAAAGGCTCCAAGGCAAGTGTGTAGAACTCCAGGCCT 3572
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3647 CCAGGCAAGTTGAGGCCCTAAATAAAAGGCTCCAAGGCAAGTGTGTAGAACTCCAGGCCT 3706

Qy       3573 CGCTGCCGGTCAGCTGCTCGGCACTTCTGCGTCAAGAGGCACTGGGGATGCAGCAGGCTG 3632
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3707 CGCTGCCGGTCAGCTGCTCGGCACTTCTGCGTCAAGAGGCACTGGGGATGCAGCAGGCTG 3766

Qy       3633 GCAGGTGGCTGGCCCTGCTAATGCAAGACTGCTCAGGCCATTTCAGCAGCAGCCAGGTGT 3692
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3767 GCAGGTGGCTGGCCCTGCTAATGCAAGACTGCTCAGGCCATTTCAGCAGCAGCCAGGTGT 3826

Qy       3693 CACCTTGGTGAGCTGGGGAAGGTGGGAAGGCACAAAGCCAGGGTTTCTACAACCACACTC 3752
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3827 CACCTTGGTGAGCTGGGGAAGGTGGGAAGGCACAAAGCCAGGGTTTCTACAACCACACTC 3886

Qy       3753 TCAGCCCGACTGACTTGCTGCGAGTGCTGGTGGAGCTCACAGACGGCGGCTGGTGGATGG 3812
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3887 TCAGCCCGACTGACTTGCTGCGAGTGCTGGTGGAGCTCACAGACGGCGGCTGGTGGATGG 3946

Qy       3813 TGGACTGTGAACCTCACTTTCCCTATGTTCAGCAGCACAAAGGGAAGAAGCCACCACATC 3872
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3947 TGGACTGTGAACCTCACTTTCCCTATGTTCAGCAGCACAAAGGGAAGAAGCCACCACATC 4006
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Qy       3873 AGCCCAGGAGCCCTGAGCAGCACAGGCAGTAGGGCCACTCACTTTGGCCATCCGCACCCA 3932
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4007 AGCCCAGGAGCCCTGAGCAGCACAGGCAGTAGGGCCACTCACTTTGGCCATCCGCACCCA 4066

Qy       3933 AATGCAATCAATCAACCCAGCTTCGGAAGCTACCCTAGGATCTCGTCAATAAACTGCTAA 3992
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4067 AATGCAATCAATCAACCCAGCTTCGGAAGCTACCCTAGGATCTCGTCAATAAACTGCTAA 4126

Qy       3993 GAAGCCATCAACTGGCCTAAAGAAAGAGTTCACTGAAGAACGCAATTGCTTTAAAGAAAG 4052
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4127 GAAGCCATCAACTGGCCTAAAGAAAGAGTTCACTGAAGAACGCAATTGCTTTAAAGAAAG 4186

Qy       4053 AAAAATTAGTTTCCTATTTAAGTCTTAAAAAAAAAGCAAACCATGTCCTGAGATGTCTGTG 4112
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4187 AAAAATTAGTTTCCTATTTAAGTCTTAAAAAAAAAGCAAACCATGTCCTGAGATGTCTGTG 4246

Qy       4113 TTAATAGTGCAGAGAGAACCTAGGGTTTGAGGTTGCTGTAGCAATGGCATTGGAGAACTT 4172
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4247 TTAATAGTGCAGAGAGAACCTAGGGTTTGAGGTTGCTGTAGCAATGGCATTGGAGAACTT 4306

Qy       4173 TAACTTGAACATTCTCATCGATACTTCCTGGACATATTT 4211
             |||||||||||||||||||||||||||||||||||||||
Db       4307 TAACTTGAACATTCTCATCGATACTTCCTGGACATATTT 4345
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Qy        572 ATCTTCGAAGCATTGAAAAGAGGCCTCAAGGAGTATCTGTGTGTGCAGCAGGCTGAGCTG 631
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        122 ATCTTCGAAGCATTGAAAAGAGGCCTCAAGGAGTATCTGTGTGTGCAGCAGGCTGAGCTG 181

Qy        632 GACCACCTGTCTGGACGCCACAAAGACACCAGGAGGAATTCCAGGCTGGCTTTCTATTAT 691
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        182 GACCACCTGTCTGGACGCCACAAAGACACCAGGAGGAATTCCAGGCTGGCTTTCTATTAT 241

Qy        692 GACCTGGACAAGCAAACGCGCTGTGTGGAAAGGCACATTCGGAAGATGGAGTTTCACATC 751
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        242 GACCTGGACAAGCAAACGCGCTGTGTGGAAAGGCACATTCGGAAGATGGAGTTTCACATC 301

Qy        752 AGCAAGGTGGATGAGCTGTACGAGGACTACTGCATCCAGTGCCGCCTGCGCGACGGCGCC 811
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        302 AGCAAGGTGGATGAGCTGTACGAGGACTACTGCATCCAGTGCCGCCTGCGCGACGGCGCC 361

Qy        812 TCCAGCATGCAGCGGGCCTTCGCCCGGTGCCCCCCGAGCCGCGCAGCCCGAGAGAGCCTG 871
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        362 TCCAGCATGCAGCGGGCCTTCGCCCGGTGCCCCCCGAGCCGCGCAGCCCGAGAGAGCCTG 421

Qy        872 CAGGAGCTGGGCCGCAGCCTGCACGAGTGCGCCGAGGACATGTGGCTCATCGAGGGGGCC 931
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        422 CAGGAGCTGGGCCGCAGCCTGCACGAGTGCGCCGAGGACATGTGGCTCATCGAGGGGGCC 481

Qy        932 CTGGAGGTTCACCTGGGCGAGTTCCACATCAGGATGAAAGGCTTGGTGGGCTACGCACGC 991
              |||||||||||||||||||||||||||||||||||||||||||||| ||||||||||||||
Db        482 CTGGAGGTTCACCTGGGCGAGTTCCACATCAGGATGAAAGGCTTGGGGGGCTACGCACGC 541

Qy        992 CTCTGTCCCGGAGACCACTATGAGGTGCTCATGCGTCTGGG 1032
              |||||||||||||||||||||||||||||||||||||||||
Db        542 CTCTGTCCCGGAGACCACTATGAGGTGCTCATGCGTCTGGG 582
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